NTP
National Toxicology Program

NTP Research Concept: Dong Quai

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Dong Quai is a complex mixture. What's in it?

- Essential oil of main root contains 91 constituents

- Alkyl phthalides
  - **Ligustilide**
  - Angelicide
  - **3-Butylidenephthalide**
- Furanocoumarin
  - Archangelicin
  - Bergapten
  - Imperatorin
- Coumarins
  - Angelol G
  - Angelicone
- Terpenes
  - Cadinene
  - Carvacrol
- Phytosterols
  - beta-sitosterol
  - Stigmasterol
- Organic acids
  - **Ferulic acid**
  - Succinic
  - Myristic
- immune-stimulating polysaccharide

Dong Quai

- Nominated by a private individual for comprehensive toxicological characterization
  - Widespread use in dietary supplements (solely or in combination)
  - Potential adverse effects during pregnancy and lactation
  - Interactive effects in individuals taking NSAIDs
- Purported effects include maintenance and balance of sex hormones, the treatment of menstrual irregularities and menopausal symptoms, and as a general tonic for the female reproductive system
- Second-highest ranked ingredient in traditional Chinese medicines
- Accurate production and import values elusive
- Regulated according to the FDA Dietary Supplement Health and Education Act of 1994

Dong Quai Toxicity

- Very limited toxicology data in the literature
- Three major components rapidly absorbed, elimination dose-dependent
- No subchronic or chronic toxicology, carcinogenicity, or reproductive and teratology studies are available in the literature for dong quai or its primary constituents
- There are conflicting results in the literature on the **estrogenic** effects of dong quai
- Constituents bergapten and psoralens may induce dermal **photosensitivity** responses
- The carcinogen safrole is present in Dong Quai essential oils
- Dong quai extracts can differential modify hepatic microsomal enzymes (P450)
- Potential interaction with drugs and dietary supplements that cause photosensitivity or affect heart rhythm, estrogenic drugs, anticoagulants, and NSAIDs

Issues and the Impact

- Commercially available solely and in a mixture with other herbs, vitamins, or minerals
- Available as fluid extracts, tinctures, decoctions, capsules, tablets, essential oil, and as dried root powder via various methods of processing leading to potential differences in the constituent profile
- Not typically normalized based on a specific component
- Since the extent of these differences is not known, serious consideration needs to be given to the **specific formulation selected for study**
- Multi-tiered research plan

Proposed Research Program

Tier I

- Investigate differences in toxicological response between various preparations of dong quai *in vivo* and *in vitro* to select **test material**
  - Series of nuclear receptor assays (ER, AR, FXR, LXR, PPAR, PXR, CAR)
    - Collaborate with the NTP Biomolecular Screening Branch
  - Other short-term tests including Hershberger and uterotrophic assays
- Develop a decision tree for selecting test material to evaluate in Tier II
  - Explore commercially available formulations
  - Determine commonly used forms or preparations
  - Conduct chemical analysis and characterization
  - Biological activity of available preparations
  - Work with botanical expert

Proposed Research Program

Tier II

- Conduct oral 14- and 90-day toxicology studies and 2-year toxicology/carcinogenicity studies in rats and mice to characterize the toxicity and carcinogenicity of dong quai
  - Consideration should be given to *in utero* and lactational exposure, blood clotting parameters
- Conduct reproductive and developmental toxicity studies with emphasis on landmarks of sexual maturation
- Conduct studies to evaluate the immunotoxicity and phototoxicity of dong quai
  - Does dong quai elicit a response similar to individual components that modulate immunity and phototoxicity?
  - Identify and quantitate photo-induced DNA adducts